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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,839	07/07/2004	Zen-ichi Terashita	3012 USOP	8728

23115 7590 07/27/2005

TAKEDA PHARMACEUTICALS NORTH AMERICA, INC
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EXAMINER

JOHNSEN, JASON H

ART UNIT	PAPER NUMBER
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1623

DATE MAILED: 07/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/500,839

Applicant(s)

TERASHITA ET AL.

Examiner

Jason H. Johnsen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 July 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-6, 8-11, 13-16, 18, 19, 21, 22 and 24 is/are rejected.
- 7) ☐ Claim(s) 7, 12, 17, 20 and 23 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on N/A is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 7/07/04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) filed on 1/11/2002.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 07/07/04 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner is considering the information disclosure statement.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 1-6, 8-11, 13, 14, and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Akiyama et al (WO 02/47723). Akiyama teaches the compounds of formula I of the instant invention where substituent R¹ is Chlorine, R² is methyl, A is a substituted benzene ring, B is an optionally substituted benzene ring, and X-Y moiety together form Ethylene-CO₂-Me or Ethylene-CO₂-Et, or Et-CO₂-Et (see examples 308, page 186, 336, page 192, and 338, page 193).
2. Claims 18, 19, and 21 are rejected under 35 U.S.C. 102(e) as being anticipated by Akiyama et al. (WO 02/47723). Akiyama teaches the compounds of formula 1, as mentioned

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above, in regressing a lipid rich plaque, as taught by claim 18, and in treating the conditions outlined in claim 19 (see page 3 of the partial machine translation).

3. Claims 15, 16, and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Akiyama et al. These claims are seen as substantial duplicates of the claims from which they depend and are therefore not further limiting. Statements of "intended use" or other similar terms meant to further define a compound or composition are not given material weight. The use of "which is a..." found in claims 15 and 16, and "for production..." found in claim 22 are descriptive examples of this policy.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims without undue experimentation. The instant disclosure is not seen to be sufficient to enable the use of compounds of Formula I and I' to **prevent the conditions outlined in the claim or to treat the broad range of diseases** without undue experimentation.

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Additionally, the instant disclosure is not seen to be sufficient to enable the use of compounds of Formula I and I' to treat all of the diseases listed in claim 19.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The breadth of the instant claims are extremely broad due to the large number of disorders which could be implicated by the regression of a lipid-rich plaque or inhibiting ACAT in a mammal. Claim 19 are seen to encompass a compound or pharmaceutically acceptable salt thereof and a method using said compound for the prevention or treatment of the host of diseases found in claim 19. Applicant has not provided sufficient evidence to support a claim drawn to all forms of disorders responsive to the partial regression of a lipid-rich plaque.

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The nature of the invention

Claim 18 is directed to a compound for the regression of a lipid-rich plaque or inhibiting ACAT in a mammal. Claim 19 is drawn to a compound for the prevention or treatment of disorders relating to lipid-rich plaque deposits such as acute coronary syndrome, coronary artery restenosis after PTCA or stent placement, peripheral artery occlusion, etc.

The state of the prior art

In the specification, on page 2, lines 15-24, Applicant indicates that many of the diseases listed in claim 19 of instant application are related closely to the characteristics of a plaque, and a lipid-rich plaque formed by deposition of a macrophage retaining lipids such as cholesterol extensively onto the inner wall of a blood vessel is believed to cause acute coronary syndrome and peripheral artery occlusion. A lipid-rich plaque formed at carotid artery or intracerebral vessel is believed to cause cerebral apoplexy or cerebral infarction. The prior art does not indicate that the instant compound is useful in preventing or treating all disorders relating to partial regression of a lipid-rich plaque.

The level of predictability in the art

The instant claimed invention is highly unpredictable. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on

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its face. In re Fisher, 427 F. 2d, 833, 166 USPQ 18 (CCPA 1970), indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Hence, in the absence of a showing of preventing or treating all the disorders in claim 19, including Alzheimer's disease, multiple risk syndrome, or metabolic syndrome, for example, by the compounds of formula I and I', one of skill in the art is unable to fully predict possible results from the administration of the compound of formula I or I', due to the unpredictability of the art pertaining to some of these disorders.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance, which would allow the skilled artisan to extrapolate from the disclosure and examples provided, to use the claimed method commensurate in the scope with the instant claims. Applicant provides limited guidance regarding the use of the instant compound in preventing all disorders listed in claim 19, or in treating such disorders as Alzheimer's disease. Applicant provides information on biological activity on pages 232-235. The data and evidence provided in the instant disclosure leads the examiner to doubt the objective truth of assertions of prevention of all the diseases in claim 19, or treatment of some of these disorders, including Alzheimer's, multiple risk syndrome, or metabolic syndrome.

The existence of working examples

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F. 2d 1557, 1562; 27 USPQ 2d 1510, 1514 (Fed. Cir.

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1993). There is not seen in the disclosure, sufficient evidence to support applicant's claims of a method for the prevention or treatment of all disorders listed in claim 19. Applicant provides evidence of the ACAT inhibiting rates of several compounds of instant application ranging in inhibition rates from .43 to 1.22. However, as taught by the applicant, inhibitors of these enzymes only shows a promising treatment for arteriosclerosis and other closely related diseases. There is not seen sufficient working examples or data from references on the prior art providing a nexus between that which applicant asserts as proof of a method for the prevention of all the diseases listed in claim 19, or the treatment of Alzheimer's, multiple risk syndrome, or metabolic syndrome.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Based on the unpredictable nature of the invention, the state of the prior art, and the extreme breadth of the claims, one skilled in the art could not use the entire scope of the claimed invention without undue experimentation. Reasonable guidance with respect to preventing or treating all the disorders of claim 19 relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of these disorders and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug treatment and subsequent knowledge of the prevention of the disease is the essence of verification of a valid preventive agent.

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It is suggested that applicant limit the disorders treatable by applicant's compounds to the treatment of arteriosclerosis related conditions that are supported in the specification by biological data, which is not seen to include Alzheimer's disease, multiple risk syndrome, and metabolic disorders.

Claim Objections

Claim 21 is objected to because of the following informalities: It contains two periods at the end of the sentence. Appropriate correction is required. Claims 7, 12, 17, 20, and 23 are objected to for depending on a rejected base claim but would be allowable if re-written in independent form. The limitations taught in these claims are not taught or fairly suggested in the prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason H. Johnsen** whose telephone number is **571-272-3106**. The examiner can normally be reached on Mon-Friday, 8:30-5:00 PM.

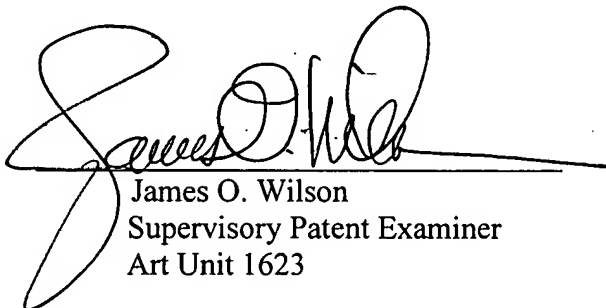
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

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system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jason H. Johnsen
Patent Examiner
Art Unit 1623



James O. Wilson
Supervisory Patent Examiner
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